UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/015,399	01/29/98	HINKKANEN	A 2328-111

HM12/1011

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EXAMINER	
VANDER VEGT, F	
ART UNIT	**PAPER NUMBER**
1644	18

DATE MAILED: 10/11/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/015,399	Applicant(s) Hinkkanen
	Examiner F. Pierre VanderVegt	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Sep 12, 2000* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), ~~or thirty days, whichever is longer,~~ from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-10 and 17-20* is/~~are~~ pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10 and 17-20* is/~~are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-10 and 17-20 are currently pending in this application.

1. In view of the amendment filed September 12, 2000, no outstanding rejections are maintained. The following are new grounds of rejection which necessitate making this Office Action NON-FINAL.

2. Upon further review by the current Examiner of record, the species requirement of the Office Action mailed May 11, 1999, to which Applicant responded by electing the species exemplified in claim 3, is hereby withdrawn.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 4, 5, 7, 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,547,669 to Rogers et al (A on form PTO-892, of record).

Briefly, base claim 1 is drawn to fusion proteins comprising epitope(s) of preproinsulin fused to epitope(s) of IA2 and/or GAD65. The '669 patent teaches fusion proteins comprising epitopes of at least two proteins and the use of such proteins to assay for T cell reactivity or antibodies to the epitopes comprising the fusion proteins. The '669 patent further teaches that the epitopes may be derived from autoantigens (see abstract, column 6, lines 1-31, column 10, lines 31-60, column 13, lines 3-30, in particular). The '669 patent also teaches that the fusion protein can comprise epitopes of autoantigens of diabetes and that such autoantigens include insulin, GAD, PM-1 and carboxypeptidase (see column 12, lines 12, lines 24-30, in particular). The '669

patent also teaches that the epitopes can be linked together by linkers comprising amino acid sequence. The '669 patent discloses that the peptide linkers can comprise protease sensitive sites such as KK (Lys-Lys) or RR (Arg-Arg), thus disclosing fusion proteins comprising two or more epitopes linked by linker comprising lysine and arginine residues as is claimed in claim 4 of the instant specification (see column 15, lines 55-67, in particular). The '669 patent further teaches that the fusion protein can be produced recombinantly or synthetically (see column 7, lines 61-67, in particular). The '669 patent discloses that the fusion protein can be made recombinantly by making cDNA encoding the fusion protein, vectors comprising said cDNA and expressing the vector in E. coli host cell (see column 19, lines 1-30, in particular). The '669 patent also teaches that the fusion protein which is provided with (comprises) a member of an affinity binding pair, histidine. (see column 19, lines 30-45, in particular). The '669 patent teaches that histidine residues allow purification of the fusion protein by binding the protein to solid phase comprising nickel (see column 19, lines 30-45, in particular). Thus a fusion protein comprising a histidine sequence is a fusion protein provided with a member of an affinity binding pair as is claimed in claim 5. The prior art teaching anticipates the claimed invention.

5. Claims 1-5, 7-10 and 17 are rejected under 35 U.S.C. 103(a) as obvious over US 5,547,669 to Rogers et al (A on form PTO-892, of record) in view of U.S. Patent No. 5,200,318 to Rabin et al (B, of record), U.S. Patent No. 5,989,551 to Maclaren et al (U2, newly cited), Hummel et al (U, of record) and Berg et al (X, of record).

The '669 patent (Rogers et al) has been discussed supra. The '669 patent does not teach fusion proteins having an epitope of the "prepro" portion of preproinsulin, IA2 or all three of IA2, GAD and preproinsulin comprising the amino acid 771-979 of IA2, amino acid 102-585 of GAD and amino acids 1-110 of PPINS. Applicant is reminded that the term "comprising" in the claim language opens up the claims to read upon a fusion protein comprising not only the recited sequences, but containing additional residues up to and including fusion proteins comprising full length IA2 and GAD.

The '318 patent (Rabin et al) teach a method of diagnosing insulin dependent diabetes with an immunoassay which utilizes an immunoreagent comprising epitopes of GAD and ICA512, which is a fragment of IA2 (see U.S. Patent No. 5,989,551 [also cited herein], column 4, lines 62-67), and ICA 12 (see abstract and claims 1-21, in particular). The '318 patent further teaches an immunoreagent that is a polymer backbone to which are attached multiples of one or more antigens and assays to determine reactivity of serum with immunoreagent (see column 7, lines 1-11 and column 7, line 24 through column 9, line 11, in particular). The '318 patent also teaches assays in which the specificity of the serum (IE reactivity to one of the antigen attached to the backbone) can be determined (see column 8, line 57 through column 9, line 9, in particular).

The '551 patent (Maclaren et al) teaches a method for detecting autoantibodies to GAD65, IA-2 and IA-2β for diagnosis of insulin-dependent diabetes mellitus (IDDM) prior to the onset of clinical presentation (column 18, line 56 through column 19, line 18 in particular). The '551 patent teaches that testing for autoantibodies to these antigens can replace the qualitative ICA assay. The '551 patent further teaches that the ICA assay typically does not detect anti-insulin antibodies (column 3, lines 32-34 in particular).

The Hummel et al reference teach that of newly diagnosed diabetes patients all showed reactivity to at least one recombinant islet cells antigen selected from insulin, GAD 65, and IA2 and that humoral and cellular immune reactivity to multiple islet cell antigens are present in patients with newly diagnosed type 1 diabetes and in high risk relatives (see abstract, in particular). Hummel et al also teaches that antibodies and cell mediated immune responses to IA2 are risk factors for the development of diabetes (see Figure 1 and 2 and page 428-429, in particular). Hummel et al further teaches that assaying for the presence of immune response to more than one autoantigen may become of increasing value in the diagnosis of preclinical type diabetes.

The combined references do not teach preproinsulin. The Berg et al reference teaches that in testing sera from patients with recent-onset diabetes, 14% of the patients sera contain insulin autoantibodies which strongly recognized recombinant preproinsulin. Berg et al also teaches that anti-GAD antibodies serve as the most relevant serological marker for ongoing β cell destruction

and that generation of insulin autoantibodies alone confers relatively little risk for IDDM development (see abstract and page 22). Berg et al teaches cDNA encoding preproinsulin and vectors and E. coli cells comprising said cDNA. The recombinant preproinsulin peptide comprises a histidine hexapeptide and GST (see page 229, in particular). Berg et al teaches that the GST moiety introduces an enterokinase site and histidine hexapeptide permits single step purification by affinity chromatography using metal chelating Sepharose charged to NI ions. (see page 229, in particular). Berg et al teaches that the use of preproinsulin to assay for autoantibodies in patients permits the detection of antibodies directed against the C-peptide or signal peptide. Berg et al further teach that 11.6% of ICA positive sera were positive for anti-preproinsulin antibodies but that none of ICA positive serum were positive for anti-insulin antibodies (see page 229 and 230, in particular).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to replace the insulin taught by the '669 patent with preproinsulin as taught by Berg et al due to the ability to detect diabetic patients reactive with the C- or signal peptides regions of the preproinsulin. It would have further been obvious to test a subject serum sample for autoantibodies versus a panel of antigens as taught by Hummel et al and the '551 patent by virtue of being able to detect move autoreactive patients because not all diabetic patients are antibody positive for all of the antigenic epitopes and to select at least preproinsulin, GAD and IA-2 as taught by the '551 patent and Hummel et al as modified by Berg et al, because they represent major autoantigens in IDDM and maximize the chances of early detection of a diabetic individual. It would have been further obvious to combine the epitopes into a single fusion protein as evidenced by the '669 patent and the '318 patent for the convenience of the practitioner. One would have been motivated to combine the teachings with a reasonable expectation of success by the teachings of the prior art that testing subject samples against preproinsulin, GAD65 and IA2 maximizes the likelihood of early diagnosis of IDDM and the general knowledge available to those in the art at the time of the invention that a single fusion protein product simplifies manufacture of a test reagent and that a single reagent would simplify

the use in 'the field' by clinical laboratories for diagnostic/evaluation purposes and allow standardization of results.

6. Claims 1-10 and 17-18 are rejected under 35 U.S.C. 103(a) as obvious over US 5,547,669 to Rogers et al (A on form PTO-892, of record) in view of U.S. Patent No. 5,200,318 to Rabin et al (B, of record), U.S. Patent No. 5,989,551 to Maclaren et al (U2, newly cited), Hummel et al (U, of record), Berg et al (X, of record) and WO 94/07464 (N, of record).

The '669, '318 and '551 patents, Hummel et al and Berg et al have been discussed supra. The invention claimed in claim 6 differs from the prior art in that the fusion protein comprises biotin or streptavidin. Here biotin is a label. However, WO 94/07464 teaches GAD labeled with biotin and the use of the biotin labeled GAD in immunoassays to detect antibodies to GAD. WO 94/07464 also teaches that autoantibodies to β-islet cell GAD may be extracted from patients serum, by binding to GAD and the complex to an insoluble or solid support. (See page 15, line 8 through page 16, line 20. Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a fusion protein comprising IA2, GAD and preproinsulin for the reasons discussed supra in which biotin is the binding member with the expectation that the biotin labeled fusion protein could be used to in immunoassays to screen sera for antibodies to IA2, GAD and preproinsulin.

7. Claims 1-5, 7-10 and 17-20 are rejected under 35 U.S.C. 103(a) as obvious over US 5,547,669 to Rogers et al (A on form PTO-892, of record) in view of U.S. Patent No. 5,200,318 to Rabin et al (B, of record), U.S. Patent No. 5,989,551 to Maclaren et al (U2, newly cited), Hummel et al (U, of record), Berg et al (X, of record) and either U.S. Patent No. 5,316,909 to Xu et al (B1, of record) or U.S. Patent No. 5,637,509 to Hemmila et al (A1, of record).

The '669, '318 and '551 patents, Hummel et al and Berg et al have been discussed supra. The invention claimed in claims 19 and 20 differs from the fusion protein discussed supra in that the label is radioactive or fluorescent (claim 19) or wherein the label is lanthanide (claim 20).

However, the labeling of reactants in an immunoassay using a label such as a lanthanide is well known in the art as evidenced by Xu et al or Hemmila et al. Xu et al teach immunoassays in which one of the reactants is labeled with a radioisotope or fluorescent. Xu et al teach that lanthanides such as europium (Eu+), terbium (Tb3+), samarium, (Sm3+) or dysprosium (Du3+) can be used to fluorescently label immunoreactants in an immunoassay (see column 1, lines 5-30 and claims 1-2, in particular). Hemmila et al teach labeling of analyte (antigen) with a lanthanide such as europium (Eu3+) or terbium (Tb3+) for use in an immunoassay (see claims 1-10, and column 7, lines 35-67, in particular).

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a fusion protein comprising IA2, GAD and preproinsulin for the reasons discussed supra and to label it with a radioactive or fluorescent label such as a lanthanide with the expectation that such a fusion protein could be used in immunoassays to screen sera for antibodies to IA2, GAD and preproinsulin.

Conclusion

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Tuesday through Friday and odd-numbered Mondays (on year 2000 366-day calender) from 6:30 am to 4:00 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
Technology Center 1600
October 5, 2000

F. PIERRE VANDERVEGT
PATENT EXAMINER